

COPY
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INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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DANEMARK

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	27.10.2004
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Applicant's or agent's file reference IPB/129186	IMPORTANT NOTIFICATION	
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International application No. PCT/IB 03/02785	International filing date (day/month/year) 14.07.2003	Priority date (day/month/year) 16.07.2002
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Applicant MEDEXIS S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IPB/129186	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB 03/02785	International filing date (day/month/year) 14.07.2003	Priority date (day/month/year) 16.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K51/12		
Applicant MEDEXIS S.A. et al.		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 08.01.2004	Date of completion of this report 27.10.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Blott, C Telephone No. +49 89 2399-7538



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IB 03/02785

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-34 as originally filed

Claims, Numbers

1-25 as originally filed

Drawings, Sheets

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IB 03/02785

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 1-25 (part)
because:
 the said international application, or the said claims Nos. 19-23 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the said claims Nos. 1-25 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the Standard.
 the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5-11, 13, 17-18, 20, 23-25
	No: Claims	1-4, 12, 14-16, 19, 21-22
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB 03/02785

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB 03/02785

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The IPEA will only formulate an assessment of novelty, inventive step and industrial applicability for the parts of the claims 1-25 for which an International Search Report has been drawn up (Rule 66.1(e) PCT) (cf. form PCT/ISA/210,box I.2).
2. Claims 19-23 relate to a subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Reference is made to the following document/s:
 - D1: SIMIONESCU L ET AL: "The development of a radioimmunoassay system for testosterone (T) and dihydrotestosterone (DHT). Part 2. The preparation of antisera to T." ENDOCRINOLOGIE. ROMANIA 1990 JUL-DEC, vol. 28, no. 3-4, July 1990 (1990-07), pages 107-125, XP008014908 ISSN: 0253-1801
 - D2: US-A-5 945 279 (POWER RONAN F ET AL) 31 August 1999 (1999-08-31)
 - D3: RAMIREZ V D ET AL: "Membrane receptors for estrogen, progesterone, and testosterone in the rat brain: fantasy or reality." CELLULAR AND MOLECULAR NEUROBIOLOGY. UNITED STATES APR 1996, vol. 16, no. 2, April 1996 (1996-04), pages 175-198, XP008014894 ISSN: 0272-4340
 - D4: BENTEN W P ET AL: "Functional testosterone receptors in plasma membranes of T cells." THE FASEB JOURNAL: OFFICIAL PUBLICATION OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY. UNITED STATES JAN 1999, vol. 13, no. 1, January 1999 (1999-01), pages 123-133, XP002234365 ISSN: 0892-6638
 - D5: US-B-6 416 7371 (MANOLAGAS STAVROS C ET AL) 9 July 2002 (2002-07-09)
 - a) In D1, anti-testosterone antisera were prepared using **testosterone-3-carboxymethyl-oxime-BSA** as antigen. The antisera may be used to measure testosterone and to detect simultaneously sera containing unusual high values of DHT.

b) D2 does not refer to conjugates.

c) In D3, steroid hormones such as **oestradiol, testosterone, progesterone derivatives conjugated to BSA** were used to investigate the existence of specific membrane binding sites in the CNS of rats.

d) D4 is a study (in-vitro tests) which provides experimental evidence for the presence of testosterone receptors on T cells. Binding sites for testosterone were localized on the plasma membrane of T cells using the ligand **testosterone-BSA-FITC** and CLSM (confocal laser scanning microscopy).

e) D5 discloses a method to increase bone strength comprising administering a bisphosphonate. The compound can be mixed with materials that supplement the desired action, such as 17-beta-oestradiol ([0154]). The anti-apoptotic effect of 17-beta-oestradiol on both osteoblasts and osteocytes is reproduced with a membrane impermeable **17-beta-oestradiol-BSA conjugate** ([0199]). SERMs such as **raloxifene or tamoxifene** may be administered in combination with the bisphosphonates ([0131]). **Osteolytic metastases** of various cancers or **multiple myeloma** are cited as representative metabolic bone diseases to be treated ([0116]). Compounds selected according to D5 can also be used as **cytostatic drugs to the skeleton, either for diagnosis or for therapeutic purposes** ([0117]).

4. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1, i.e. the use of steroids conjugated with mammalian proteins in the treatment of solid cancers or haematological malignancies is not novel over D5 in the sense of Article 33(2) PCT (cf. item 3.e)). This applies mutatis mutandis to claims 2-4, 12, 14-16, 19, 21-22.
5. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5-11, 13, 17-18, 20, 23-25 does not involve an inventive step over D5 in the sense of Article 33(3) PCT.

The document D5 is regarded as being the closest prior art document. D5 discloses a method to increase bone strength comprising administering a bisphosphonate. The compound can be mixed with materials that supplement the desired action, such as 17-beta-oestradiol ([0154]). The anti-apoptotic effect of 17-beta-oestradiol on both

osteoblasts and osteocytes is reproduced with a membrane impermeable **17-beta-oestradiol-BSA conjugate** ([0199]).

According to D5, drugs used in the treatment of osteoporosis such as **oestrogens** or progesterone, SERMs such as **raloxifene or tamoxifene** etc can be administered in combination with the bisphosphonates ([0131]).

Osteolytic metastases of various cancers or **multiple myeloma** are cited as representative metabolic bone diseases to be treated ([0116]).

Compounds selected according to D5 can also be used as **cytostatic drugs to the skeleton, either for diagnosis or for therapeutic purposes** ([0117]).

Compositions comprising biphosphonates together with further drugs such as **oestrogens** or progesterone, SERMs such as **raloxifene or tamoxifene** etc are merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed in D5, i.e. the strengthening of bones and decrease of bone fragility in diseases like **osteolytic metastases** of various cancers or **multiple myeloma**...

The subject-matter of claim 13, i.e. a composition comprising a steroid conjugated with a protein and a cytoskeleton acting drug such as taxol does therefore not involve an inventive step. This applies mutatis mutandis to claims 5-11, 17-18, 20, 23-25.

6. Industrial applicability

For the assessment of the present claims 19-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.